

08/123,936 filed September 17, 1993, issued as U.S. Patent No. 5,726,014 on March 10, 1998; which is a continuation-in-part of U.S. Application No. 07/996,783 filed December 23, 1992, issued as U.S. Patent No. 5,693,463 on December 2, 1997; which is a continuation-in-part of U.S. Application No. 07/723,618 filed June 27, 1991, now abandoned, each of which is expressly incorporated by reference herein.

The Table of Contents found at page i, line 8 through page iii, line 25 has been deleted.

The paragraph beginning on page 11, line 1, has been replaced with the following rewritten paragraph.

Figure 4 shows the incorporation of biotin and digoxigenin into a typical oligonucleotide (SEQ ID NO: 614) molecule for use in the assay of the present invention. The oligonucleotide contains the binding sequence (i.e., the screening sequence) of the UL9 protein, which is underlined, and test sequences flanking the screening sequence. Figure 4 also shows the preparation of double-stranded oligonucleotides end-labeled with either digoxigenin or 32P (SEQ ID NO: 614-DDD).

On page 11, replace the paragraph starting on line 7 with the following:

Figure 5 shows a series of sequences that have been tested in the assay of the present invention for the binding of sequence-specific small molecules. Test sequences shown are: UL9Z1, SEQ ID NO: 603; UL9Z2, SEQ ID NO: 604; UL9 CCCG, SEQ ID NO: 605; UL9 GGGC, SEQ ID NO: 606; UL9 ATAT, SEQ ID NO: 607; UL9 polyA, SEQ ID NO: 608; UL9 polyT, SEQ ID NO: 609; UL9 GCAC, SEQ ID NO: 610; ATori-1, SEQ ID NO: 611; oriEco2, SEQ ID NO: 612; oriEco3, SEQ ID NO: 613.

On page 12, replace the paragraph starting on line 1 with the following:

Figure 12 demonstrates a test matrix based on DNA:protein-binding data. Test oligonucleotides shown have the sequences identified as SEQ ID NO: 643 to SEQ ID NO: 654.

On page 13, please replace the paragraph starting on line 6 with the following:

Figure 26 shows examples of bis-distamycin target sequences for bis-distamycins with internal flexible and/or variable length linkers targeted to sites comprised of two TTCC sequences, where N is any base. Test sequences are identified as SEQ ID NO: 655 to SEQ ID NO: 658.

On page 13, please replace the paragraph starting on line 9 with the following:

Figures 27A to 27H show sample oligonucleotides for competition binding studies using the assay of the present invention. Test sequences are identified as SEQ ID NO: 621 to SEQ ID NO: 624.

On page 13, please replace the paragraph starting on line 11 with the following:

Figure 28 shows the DNA sequences of the HIV pro-viral promoter region (SEQ ID NO: 627). Several transcription factor binding sites are marked.

On page 13, please replace the paragraph starting on line 13 with the following:

Figures 29A to 29D illustrate sample test oligonucleotides for use in the polymerase chain reaction based selection technique of the present invention. In Figure 29A, X is the number of bases that comprise the test site. Oligonucleotides are identified as SEQ ID NOs: 630-632 (29A), SEQ ID NO: 633 (29B), SEQ ID NO: 634 (29C) and SEQ ID NO: 635 (29D).

On page 13, please replace the paragraph starting on line 16 with the following:

Figure 30 illustrates a sample test oligonucleotide for use in the assay of the present invention, where the test oligonucleotide employs several different DNA:protein interaction systems. Illustrated oligonucleotides are identified as SEQ ID NOs: 636-640.

On page 13, please replace the paragraph starting on line 19 with the following:

Figure 31 illustrates the results of screening a selected test sequence with a single DNA:protein interaction system. In the figure, the test site is shown in bold, the potential binding site for the test molecule is underlined. Test sequences are identified as SEQ ID NO: 659 to SEQ ID NO: 661.

On page 13, please replace the paragraph starting on line 22 with the following:

Figure 32 illustrates the results of screening the same selected test sequence as shown in Figure 31, but using a different single DNA:protein interaction system. In the figure, the test site is shown in bold, the potential binding site for the test molecule is underlined. Test sequences are identified as SEQ ID NO: 662 to SEQ ID NO: 664.

On page 42, please replace the paragraph starting on line 10 with the following:

One example of test oligonucleotides using several different DNA:protein interaction systems are shown in Figure 30. The top strands of the pool of test oligonucleotides shown in Figure 30 have 6 base pair test sequences (NNNNNN) and represent synthetic pools of all possible 4096 test sequences. The remainder of the nucleotide sequence is fixed. The test oligonucleotides contain the UL9 recognition sequence, 5'-CGTTCGCACTT-3' (SEQ ID NO: 601) (underlined) on one side of the test sequence and a restriction endonuclease binding sequence, 5'-GGTACC-3' (bold), on the other side of the test site. The restriction endonuclease recognition sequence is recognized by the three different restriction endonucleases Asp718, RsaI and KpnI. In Figure 30 the UL9 binding site (screening sequence) is located 3' of the test sequence: the UL9 binding site (screening sequence) can also be located 5' of the test sequence.

On page 114, please replace the paragraph starting on line 27 with the following:

The same argument can be extended to trimer molecules: the trimer of X, X3, would bind a 12 bp sequence, 5'-ACGTACGTACGT-3'/5'-ACGTACGTACGT-3', (SEQ ID NO: 642) with a theoretical equilibrium affinity constant of $8 \times 10^{15} \text{M}^{-2}$.

On page 158, please replace the paragraph starting on line 27 with the following:

The following is a description of how selected promoter sites were located in the public database from "EMBL." The flat field annotations from "EMBL" Version 32 as processed by "INTELLIGENETICS" (Mountain View, CA), were obtained with the set of UNIX programs call "IG-SUITE." These programs were executed on a "SUN IPX" workstation. An AWK script was used to parse all the primate annotation files listed in the "EMBL" database. The AWK interpreter is supplied as part of the system software that comes with the "SUN IPX" workstation.

On page 11, please replace the paragraph starting on line 17 with the following:

Figures 9A-9B present data demonstrating the effect on UL9-COOH binding of alterations in the test sequences that flank the UL9 screening sequence.

On page 12, please replace the paragraph starting on line 2 with the following:

Figures 13A-13B list the top strands (5'-3') of all the possible four base pair sequences that could be used as a defined set of ordered test sequences in the assay.